REMARKS

Per the Office Action dated December 11, 2007, claims 66, 67, 87-94, 101, and 133-141 were examined. Claims 66, 67, 87-94, 101, and 133-141 were rejected.

In the instant Amendment and Response, Applicant has amended independent claim 66 to correct a typographical error. Entry of the instant amendment is respectfully requested.

Before addressing the instant rejections, Applicant would like to reiterate several key features of the claimed invention. Briefly, the Applicant lays claim to a very specific particle for which the inventor has been able to demonstrate unique and improved properties relative to prior art delivery vehicles. The claimed invention comprises a micelle comprising a therapeutic bioactive component and hydrophobic surfactant, with a surrounding precipitate shell comprising a polypeptide ligand and a precipitating cation, that results in a nanocapsule of less than about 50 nanometers in diameter capable of receptor mediated targeting and uptake into the cell. The claimed invention provides the first mechanically-stabilized sub-50 nm targeted particle encapsulating a therapeutic bioactive component.

The ultrasmall size of this unique composition is enabled in part by the core being formed by a transiently stable hydrophobic micelle; stabilization and targeting are efficiently provided by the precipitate polypeptide shell. The problems that are simultaneously addressed by the claimed invention include, for example, delivery of a therapeutic cargo intact into the cell by protecting the cargo from enzymatic degradation and by avoiding lysosomal degradation, in a cell targeted manner. Importantly, avoiding lysosomal degradation has been recognized in the art as a major obstacle to new, important therapies (see, for example, Varga et al.: lysosomal degradation is "believed to be the greatest barrier for successful gene expression in non-viral delivery vehicles."[1]) All publications discussed herein are attached to an IDS submitted together with this instant response, under separate cover.

Applicant respectfully requests that the Examiner consider these discussions as an aid to understanding the state of the prior art and the inventive contributions of the

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[1] C.M. Varga, et al. "Receptor Mediated Targeting of Gene Delivery Vectors: Insights from Molecular Mechanisms for Improved Vehicle Design", *Biotechnology and Bioengineering*: 70(6) 593-605 (2000).

Applicant to the art of targeted non-viral delivery vehicles for bioactive agents. Applicant now turns to a discussion of the instant rejections, hereinbelow.

DOUBLE PATENTING

The Examiner has provisionally rejected the claims 66, 67, 87, 88, 90, 94, 134 and 136-141 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-28 of copending Application no. 11/622,359. Office Action page 4.

The Examiner has provisionally rejected the claims 66, 67, 87, 88, 90, 94, 133, 134 and 136-141 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 13 of copending Application No. 10/958,999. Office Action page 6.

The Examiner has also rejected the claims 66, 67, 87, 88, 90, 93, 94, 133, 134, and 136-141 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29 and 42 of U.S. Patent No. 6,632,671. Office Action page 8.

The present application has an earlier priority date than co-pending Application No. 11/622,359 and 10/958,999, and the same priority date as U.S. Patent No. 6,632,671.

Applicant acknowledges these rejections and wishes to advise that Application No. 10/958,999 has been abandoned, and its continuation was filed 2/7/08 (Application No. 12/027,863). Applicant will address the Examiner's double patenting rejections once all other rejections have been resolved, or earlier.

CLAIM REJECTIONS UNDER 35 U.S.C. § 102(e)

The Examiner has renewed the rejection of claims 66, 67, 87, 88, 90-94, and 135, and applies the rejection to new claims 137-139, as being anticipated by Unger, E.C. et al. (U.S. Patent No. 6,139,819, the "Unger et al" patent). The Examiner contends that "Unger et al. teach particles comprising a core provided by monomolecular layers of surfactant micelles consisting of a surfactant such as cetyl alcohol (i.e., a non-ionic surfactant having an HLB less than 5.0) and a bioactive agent which has a therapeutic effect, wherein the micelles are stabilized by a surrounding protein shell; the protein shell is covalently coupled with targeting ligands that bind cell surface receptors (i.e., the protein provides

specific cellular uptake), wherein the covalent coupling involves the formation of Schiff base linkages which are reduced by using lithium aluminum hydride" (Office Action, page 11). The Examiner also contends that Unger et al. teach that the particles have a size of about 30 nm and a hollow core comprising the bioactive agent, the particles can be in the form of nanocapsules, the particles can comprise a combination of two or more surfactants, a biocompatible oil, a water miscible solvent, and a polynucleic acid condensing agent (Office Action, pages 11-12). The Examiner also contends Unger et al's particles inherently possess a lithium-precipitated protein shell, since "the covalent attachment of the targeting ligand requires addition of lithium aluminum hydride (see above), which would necessarily result in a precipitated protein shell", and notes that lithium is known in the art as a protein precipitating agent, citing for example Kondo et al Abstract (Office Action, page 12). The Examiner contends that Unger et al. teach all of the limitations of the instant claims and accordingly the claimed invention is anticipated. The Examiner did not find Applicant's previously-submitted arguments in the Amendment entered 9/26/2007 persuasive.

Applicant traverses this rejection. In addition to the arguments and case law discussed by the Applicant in the September 26, 2007 response, all of which are incorporated herein by reference in their entireties, Applicant wishes to bring to the Examiner's attention that the Examiner's position is untenable in view of the previously-submitted case law, as well as in view of two Board of Patent Appeals and Interferences ("Board") decisions. One very recent Board decision, decided February 29, 2008, believed to be binding precedent, affirms the relevance of Applicant's arguments that "picking and choosing" is not the proper standard of anticipation. *Ex parte Lettman*, Appeal No. 2008-1185. Applicant also brings to the Examiner's attention another especially relevant Board decision. In this decision, while non-binding, the Board found that another E. Unger (same first inventor) patent with similar broad disclosure as the instantly cited Unger et al. patent, is not anticipatory because the claimed invention did not fit the "pattern of preferences" disclosed by the E. Unger patent . *Ex parte Basu*, Appeal No. 2005-1152. Both decisions reversed a holding of anticipation under 35 U.S.C. § 102(b). Both decisions are appended to the end of this instant Office Action Response.

These decisions show that in the instant case, contrary to the allegations of the Examiner, the cited reference Unger et al. does not rise to the level of an anticipation, under the body of law provided by the courts and further under the decisions made by the Board.

Ex parte Lettman affirms the well-settled principle that "if a reference does not disclose a specific embodiment which satisfies all of the claim limitations, the reference will nonetheless describe the claimed invention within the meaning of Section 102(b) [ONLY] if it 'clearly and unequivocally ... [directs] those skilled in the art to [the claimed invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.' Whether a reference provides clear and unequivocal direction to the claimed invention is determined on the total circumstances with respect to the disclosure of the reference . . .[s]uch direction is provided to one of ordinary skill in the art where the totality of the reference provides a "pattern of preferences" which describes the claimed invention without the necessity for judicious selection from various disclosures thereof." (Citations omitted) (*Ex parte Lettmann,* Appeal 2008-1185, p. 6.) In other words, if an invention is not disclosed in a specific embodiment by the alleged reference, it must then clearly and unequivocably, within the "pattern of preferences" disclosed by the reference, disclose the claimed invention.

In the instant case, Applicant respectfully submits that not only does Unger et al. not disclose a specific embodiment that satisfies all of the claim limitations, Unger et al. does not disclosed the required "the pattern of preferences" for a *prima facie* case of anticipation. Applicant respectfully submits that the Examiner's choosing of several elements from the vast disclosure of Unger et al is not sufficient to establish anticipation to the exclusion of considering whether one of ordinary skill in the art would envisage the instant claimed invention in complete and exact terms upon reading Unger et al.

Turning more specifically to *Ex parte Basu*, the examiner rejected a claim directed to administering to the respiratory tract a bioactive agent in association with a charged lipid, wherein the lipid had an overall net positive charge with a net negative charge upon association, wherein the agent was not a nucleic acid and the release of the agent is sustained, over E.C. Unger et al U.S. Patent No. 5, 830,430 (same first inventor as the Unger et al reference of the present prosecution. The examiner's rejection was reversed with the following reasoning:

> [W]e agree with appellants that the many variables present within the disclosure of Unger weaken any alleged *prima facie* case of anticipation alleged by the examiner....We do not find that the examiner has pointed to any one specific example in the disclosure of Unger which anticipates the claimed method, or has indicated why the claimed choices would have been preferred from reading the disclosure of Unger...Therefore we agree with appellants that the examiner has failed to establish a *prima facie* case of anticipation on the facts before us. (*Ex parte Basu,* Appeal 2005-1152, pp. 6-7)

Summarizing Applicant's arguments which are presented in more detail below, Applicant submits the facts and issues of *Ex parte Basu*, as summarized by the Board, are highly similar to those in the instant prosecution. Specifically, both the E. Unger '430 and '819 disclosures describe a large number of highly variable elements that can be combined in an almost limitless number of possible combinations; both the '430 and '819 disclosures lack any specific example that anticipate the claims at issue in *Ex parte Basu* (as well as the instant claims); and in both *Ex parte Basu* and in the present Office Action, there is no support for the argument that the elements recited by the respective Examiners would have been recognized as preferred by one skilled in the art upon reading the '430 and '819 disclosures. Applicant submits the similarity between the instant case and *Ex parte Basu* shows *Ex parte Basu* is highly relevant to the instant case, and the Examiner is requested to consider the outcome of any future appeal in the instant case based on the Board decisions cited herein.

Unger et al Does Not Teach a Specific Embodiment of the Claimed Invention

The first test of anticipation, based upon case law as succinctly summarized in *Ex parte Lettmann* and echoed in *Ex parte Basu*, is to determine if the reference discloses a specific embodiment which satisfies all the limitations of the claimed invention. The reference embodiment must be in the full detail and presented order of the claimed invention. In the instant case, Unger et al does not disclose such an embodiment – i.e., as disclosed in claim 66 relating to a surfactant micelle comprising a therapeutic bioactive component and a hydrophobic surfactant, surrounded by a precipitate shell comprised of a polypeptide and a cationic precipitating agent, which provides cell-targeted delivery and uptake via receptor mediation, in a capsule measuring less than about 50 nanometers in

diameter. Claim 138 repeats these limitations, and adds the limitation that the cationic precipitating agent is Li+.

It is respectfully submitted that the smallest particle disclosed in Unger et al's examples is a simple albumin-glutaraldehyde mixture that is at least 4 times the size (200 nanometers) of the nanocapsules of Applicant's claim 66, and this prophetic example (39A) discloses neither a hydrophobic surfactant nor a precipitate shell comprising a polypeptide and cationic precipating agent. Therefore a specific embodiment of the present invention is not taught by Unger et al.

Unger et al Does Not Direct the Ordinary Artisan to the Claimed Invention

As discussed above, it is well established that if a reference does not disclose a specific embodiment of the claimed invention, a second test of anticipation is available – in terms of the instant case, the test is to determine if Unger et al direct the ordinary artisan to the instant claimed invention, assessing whether the totality of Unger et al "provides a 'pattern of preferences' which describes the claimed invention without the necessity for judicious selection from various disclosures thereof." *Ex Parte Lettman*, Appeal 2008-1185, page 6. If the determination is negative, anticipation is not established.

Applicant submits an ordinary artisan would not envisage the instant claimed invention in view of Unger et al's disclosed pattern of preferences, as described in more detail below.

The following discussion relates to Unger et al's pattern of preferences. Applicant submits Unger et al as a whole teaches 200 nm-to micron-sized formulations of inert gas or gaseous precursors encapsulated in flexible lipids for use in conjunction with ultrasound that can visualize or rupture said formulation at a targeted extracellular site. This characterization is supported for example by the following disclosures in Unger et al.

> [T]here is a need for improved ultrasound techniques, including improved contrast agents which are capable of providing medically useful images.... (Col 3, lines 66-67, and Col.4, lines 1-2) ¶ [B]ubbles, including gas-filled bubbles, are useful as contrast agents. The term "bubbles", as used herein, refers to vesicles which are generally characterized by the presence of one or more membranes or walls surrounding an internal void that is filled with a gas or precursor thereto. Exemplary bubbles include, for example, liposomes, micelles and the like. As discussed more fully hereinafter, the effectiveness of bubbles as contrast agents depends upon various factors,

including, for example, the size and/or elasticity of the bubble. ¶ With respect to the effect of bubble size, the following discussion is provided. As known to the skilled artisan, the signal which is reflected off of a bubble is a function of the radius (r.sup.6) of the bubble (Rayleigh Scatterer). Thus, in the frequency range of diagnostic ultrasound, a bubble having a diameter of 4 micrometer (.mu.m) possesses about 64 times the scattering ability of a bubble having a diameter of 2 µm. Thus, generally speaking, the larger the bubble, the greater the reflected signal. ¶ However, bubble size is limited by the diameter of capillaries through which the bubbles must pass. Generally, contrast agents which comprise bubbles having a diameter of greater than 10 µm can be dangerous since microvessels may be occluded. Accordingly, it is desired that greater than about 99% of the bubbles in a contrast agent have a diameter of less than 10 µm. **Mean bubble diameter is important also, and should be greater than 1 µm, with greater than 2 µm being preferred. The volume weighted mean diameter of the bubbles should be about 7 to 10 micrometer**. ¶ The elasticity of bubbles is also important. This is because highly elastic bubbles can deform, as necessary, to "squeeze" though capillaries and/or to permit the flow of blood around the bubbles. This decreases the likelihood of occlusion. (Col. 4, lines 6-41)… ¶ Accordingly, new and/or better contrast agents and methods for providing same are needed. The present invention is directed to this, as well as other important ends. (Col 5, line 56-58) (emphasis added)

Applicant's characterization of Unger et al's teaching as a whole is further supported by the reference's pattern of preferences, as reflected in the specification:

Unger et al preference (emphases added)	Source
1. Materials from which the vesicles are constructed are preferably biocompatible lipid, protein or polymer materials,	Col 30, lines 59-61
2. Of these materials, the biocompatible lipids are preferred.	Col 30, lines 61-62
3 Preferred lipid materials are those that are flexible, such that "the vesicles can alter their shape, for example, to pass through an opening having a diameter that is smaller than the diameter of the vesicle."	Col. 17, lines 44-49
4. The vesicles "preferably contain a gas or gaseous precursor"	Col 8, lines 24-25
5. It is "especially preferred" that the internal void be filled 100% with a gas or gaseous precursor	Col 8, lines 42-43
6. "The gas provides the lipid-based compositions with enhanced reflectivity, particularly in connection with vesicle compositions in which the gas is entrapped within the vesicles. This may increase their effectiveness as contrast agents."	Col 23, lines 38-43
7. Preferred gases are those which are inert and biocompatible, with perfluorocarbons being both preferred gases and gaseous precursors as well as a preferred stabilizing compound.	Col 23, lines 44-45, Col 26, lines 31-32, Col. 27, lines 44-52, Col. 29, lines 56-58
8. Most preferred "vesicle" size is 200 nm to about 7 um ("Vesicles" are broadly defined as "spherical entities comprising one or more walls or more membranes which form one or more internal voids" and include "liposomes, micelles, bubbles, microbubbles, microspheres, lipid-, polymer- protein- and/or surfactant-coated	Col. 7, lines 28-59, Col. 28, line 57

bubbles, microbubbles and/or microspheres, microballoons, aerogels, clathrate bound vesicles, and the like".)	
9. In preferred embodiments, targeted compounds are incorporated in compositions which are used to form targeted vesicles, and changes, for example, in pH and/or temperature in vivo, may be employed to promote a change in location in the targeting ligands, for example, from a location within the vesicle, to a location external to the outer wall of the vesicle, or that high energy ultrasound can also be used to rupture the vesicle to expose the targeting ligand to the binding site.	Col. 53, lines 42-51 and Col. 54, lines 32-44
10. Compositions of the present invention are particularly useful in connection with ultrasound, including diagnostic and therapeutic ultrasound, and that the use of the compositions with ultrasound is "described throughout the present disclosure".	Col. 55, lines 1-5
11. For example, ultrasound may be used to visualize the vesicles and verify the localization of the vesicles in certain tissue. In addition, ultrasound may be used to promote rupture of the vesicles once the vesicles reach the intended target, including tissue and/or receptor destination, thus releasing a bioactive agent and/or diagnostic agent.	Col. 81, lines 64-67, and Col 82, lines 1-2
12. As a preferred embodiment of the invention, gas filled vesicles are targeted to atherosclerotic plaque to noninvasively detect diseased blood vessels before damage has occurred.	Col. 36, lines 64-67
13. Ligands targeting receptors are "desirably capable of targeting GPIIbIIIa receptors". The most preferred targeting ligands are those which will target a plasma membrane associated GPIIbIIIa in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to GPIIbIIIa. Preferred targeting ligands for the GPIIbIIIa receptor are peptides. [2]	Col. 34, lines 53-55, Col. 37, lines25-29, Col. 41, lines 66-67

Unger et al.'s "pattern of preferences" contrasts markedly with Applicant's claims 66 and 138. Examiner's finding of anticipation necessarily requires that one of ordinary skill in the art would be directed by Unger et al.'s preferred-pattern of disclosures and examples, in clear and unequivocal terms, to envision, for example, the use of: a therapeutic bioactive agent of the claimed invention *vs.* the reference's preferred inert gas (see Table above, lines 4-5); a surfactant micelle comprising a therapeutic bioactive agent and a hydrophobic surfactant (lipid) *vs.* the reference's preferred vesicle comprising a lipid (hydrophobic or hydrophilic – the reference states no preference) with a void that is filled with inert gas or gaseous precursors (see Table above, lines 5 and 8); a precipitate shell comprising a polypeptide and a cation lithium, *vs.* the reference's preferred lipid (with no mention of a precipitating cation lithium) that will impart size-altering flexibility to the vesicle (see Table above, line 3); and receptor-based uptake *vs.* the reference's preference

[2] Unger et al Example 60 describes use of such ligands in general detail. More detail of use of a microbubble with a peptide targeting the GPIIaIIIA receptor is provided in Wu, Unger, et al (1998) *Investigative Radiology* 880-885. Gas-filled, *3 um sized* microbubbles were shown to facilitate treatment of blood clots by ultrasound, where therapeutic effect is achieved by dissolving the clots rather than breaking them into fragments. The

of using ultrasound to rupture the vesicle outside the cell (see Table above, lines 10-11); and doing all of this so as to achieve the precise combination of the claimed invention.

Further, Applicant submits that Unger et al. provides no clear and unequivocal direction such that an artisan of ordinary skill could make a "vesicle" with a size of 30 nanometers (Col. 28, line 52) and in all other aspects identical to the instantly claimed composition, particularly in view of Unger et al.'s teaching that the most preferred "vesicle" size is 200 nm to about 7 um (see Table above, line 8) and in view of Unger et al.s' defining "vesicle" as "liposomes, micelles, bubbles, microbubbles, microspheres, lipid-, polymer- protein- and/or surfactant-coated bubbles, microbubbles and/or microspheres, microballoons, aerogels, clathrate bound vesicles, and the like", and teaching that all of which may *or may not* include a bioactive agent, and all of which may *or may not* include a targeting ligand (see Table above, line 8). This definition is so broad, it would be impossible for one of ordinary skill in the art to envisage what specific "vesicle" embodiment is being disclosed with respect to this minimum size. An artisan of ordinary skill might then look to Unger et al.s' Examples for further information, and upon doing so, that artisan would be guided even further away from the compositions of the instant claims.

In view of the above, Applicant submits it is improbable that one of ordinary skill in the art would envision the instant invention upon the reading of Unger et al.

Accordingly, it is clear that no supportable case has been made to establish a *prima facie* case of anticipation, for the reason that not only does Unger et al. not disclose a specific embodiment that satisfies all of the claim limitations, Unger et al. does not disclose the required "the pattern of preferences" for a *prima facie* case of anticipation. Applicant respectfully submits that the Examiner's choosing of several elements from the vast disclosure of Unger et al is not sufficient to establish anticipation to the exclusion of considering whether one of ordinary skill in the art would envisage the instant claimed invention in complete and exact terms upon reading Unger et al.

Reconsideration is respectfully requested.

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authors report treatment of blood clots with microbubbles + ultrasound, + a thrombolytic drug administered *independent* of the microbubble, was also effective.

Unger et al Does Not Inherently Teach the Claimed Invention

The Examiner also contended that Unger et al "inherently" teaches a precipitate shell comprising a polypeptide and cationic precipitating agent, such as lithium. Specifically, the Examiner states:

> "Unger et al teach…the protein shell is covalently coupled with targeting ligands that bind cell surface receptors (i.e., the protein provides specific cellular uptake), wherein the covalent coupling involves the formation of Schiff base linkages which are reduced by using lithium aluminum hydride….With respect to the limitation of the protein shell being precipitated by the cation, wherein the cation is Li+ (claims 66 and 139), this is inherent to the nanocapsules of Unger et. al., since the covalent attachment of the targeting ligand requires addition of lithium aluminum hydride (see above) which would necessarily result in a precipitated shell (it is noted that Li+ is known in the art as a protein precipitating agent, see for example Kondo et. al. Abstract). Since Unger et. al teaches all the limitation of the instant claims, the claimed invention is anticipated by the above-cited art." (Office Action, pages 11 and 12)

It is submitted that the Examiner's assertion that the covalent attachment of the targeting ligand using LAH would inherently result in a precipitate shell comprising protein and lithium (claim 138 and 139) is misplaced and contradictory to accepted scientific principles. The instant application teaches a precipitate shell formed by using aqueous ions (including, for example, lithium) to displace solute bonding to water (i.e., a phenomenon known as "salting out"). One skilled in the art would understand the resulting precipitate shell would be comprised of for example a polypeptide and ions (including for example lithium).

In contrast, Unger et al teaches the use of the reducing agent lithium aluminum hydride (LAH) to render more permanent, Schiffs-base linkages for covalently coupling ligands to for example lipids. (A second reducing agent, lithium aluminum diisobutyl hydride (DIBAL), is also listed in Unger et al, but one skilled in the art would recognize the use of the term "lithium" here to be incorrect, as DIBAL contains no lithium and is thus only an aluminum analog of LAH.) The reference (taken with Kondo) is <u>not</u> equivalent to the claimed lithium precipitate, for several reasons. First, it is well known in the art that LAH is a highly reactive and nonselective reducing agent such that a conventional practice is to expose the final product (for example the desired ligand conjugate) to LAH for only

30 minutes, in order to degrade it for thin layer chromatography analysis (Thompson & Lee (1965) BBA 55068:151-9; Wood & Snyder (1967) Lipids 3(20:129-35). LAH reacts explosively with water, and thus conjugations using LAH are executed in water-insoluble ether, followed by careful dropwise addition of water to decompose the LAH into its subcomponents (lithium ion, aluminum ion and hydrogen gas), followed by separation of the desired final conjugation product away from the water-soluble lithium by multiple extractions with ether (Nystrom & Brown (1947) *JACS* 69:2548-9; Smith & Ho (1972) *JOC* 37(4):653-6). Therefore, to avoid degradation of the product conjugate, one skilled in the art would purify the desired product conjugate (e.g., ligand) away from lithium. Second, it is well established that LAH-mediated reduction reactions are effected by transferring the negative hydride anion, and not the positive lithium cation, to the product (Nystrom & Brown (1947) *JACS* 69:2548-9; Smith & Ho (1972) *JOC* 37(4):653-6). Thus lithium is a reaction side product, not a part of the final product. Third, with respect to Kondo et. al, the authors describe the use of lithium chloride in a process to purify DNA plasmid away from cellular RNA and protein. The claimed invention does not teach the use of lithium to remove RNA and protein from DNA. Rather, the claimed invention teaches the use of lithium to stabilize nanocapsules comprising for example DNA cargo and a protein shell.

It is well established that to determine anticipation under the theory of inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). "[T]he examiner must provide a basis in fact and/or technical reasoning to necessarily support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (BPAI 1990) Examiner has not properly supported the assertion that a shell comprising a lithium precipitate is inherent in Unger et al., by articulating a rationale grounded by appropriate scientific principle. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient" (re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981). Therefore a prima facie case of anticipation has not been established.

Unger et al's Particle Size Range Is Not Taught With Sufficient Specificity To Anticipate The Claimed Invention

On page 15 of the Office Action, Examiner states

> with respect to size, it is noted that, beside the range of 30 nm – 100 um, Unger et al clearly teach the specific embodiments of 30 nm and 12 nm (Col. 28, lines 60-62).

Applicant first notes that a review of Unger et al's description at Col 28, lines 60-62 reveals disclosure of vesicles comprising diameters of 30 um and 12 um, not 30 nm and 12 nm as asserted by the Examiner. It is submitted that any generic disclosure of small sizes in Unger et al. does not support a *prima facie* anticipation of the claimed invention, based upon requirements for the reference to provide clear and unequivocal direction to the invention.

Applicant also notes that Applicant's prior arguments with respect to range of particle size not being taught with sufficient specificity by Unger et al, as made in Responses entered 1/5/07 and 9/26/07, have never been addressed by the Examiner. Below, Applicant summarizes Applicant's previously submitted arguments, with the entire argument from Applicant's Responses having been incorporated by reference herein in their entireties.

MPEP § 2131.03(II) states that "[w]hen the prior art discloses a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation." The disclosed size range of Unger's vesicles is between 30 nanometers and about 100 micrometers, allegedly overlapping Applicant's claimed size of less than about 50 nanometers. However, none of the Examples in Unger et al. disclose a vesicle of less than about 200 nanometers. Accordingly, the instant situation falls squarely within the scope of this section of the MPEP, necessitating that the Examiner undertake a determination as to anticipation specific to this particular case.

The MPEP then continues (at § 2131.03(II)), "If the claims are directed to a narrow range, and the reference teaches a broad range, . . . it may be reasonable to conclude that the narrow range is not disclosed with 'specific specificity' to constitute an anticipation

of the claim," *citing Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

In *Atofina*, the court held that the disclosure in the prior art was only that of a range, not a specific temperature in that range, and "the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points." *Atofina*, 441 F.3d. Applicant's claimed size is a specific species of all possible size ranges of particles. Importantly, the size species claimed by Applicant is the size cutoff for efficient caveolae uptake of Applicant's particles into cells, allowing for avoidance of destruction of the particles by lysosomes within the cells (e.g., see Example 2 of the instant specification). In contrast, Unger et al. provides no similar description of his stated 30 nm threshold. In view of the above, it is evident the size of 30 nm is in fact only a generic disclosure of Unger et al. Therefore, it is submitted that Unger et al. does not disclose the claimed range and does not serve as an anticipation of Applicant's claims.

The Claimed Invention is Not Anticipated by Unger et al

In view of the above, Applicant respectfully submits Examiner has not established by a preponderance of evidence a prima facie case that Unger et al anticipates the claimed invention. This rejection under 35 U.S.C. § 102(e) should be withdrawn and such action is respectfully requested.

Other Considerations

Applicant's previous arguments as presented in the Response entered September 26, 2007 are hereby incorporated into the instant Response by reference in their entireties. Some arguments are reiterated specifically herein as well.

Applicant provides a specific rebuttal to the Examiner's specific contention regarding intracellular delivery as discussed below.

With respect to Examiner's assertion that Unger et al teaches their "nanocapsules" as being suitable for the intracellular delivery of DNA, as evidenced by Example 42 (Office Action, page 15), Applicant respectfully submits the particle in the cited example is a simple cationic liposome of undefined size, and not the composition of the claimed invention. Moreover, there is no disclosure in this example or in the reference as a whole

that would direct one skilled in the art from this cationic liposome to the claimed invention. Applicant therefore submits Examiner's response does not establish or support that Unger et al directs one of ordinary skill in the art to the claimed invention.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103

Claims 66, 67, 87, 88-94, 133-135, and 137-141 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Unger et al taken with Kondo et al., in view of Schneider et al FEBS Letters, 1998, 429: 269-273, of record). See Office Action at page 16. The Examiner cites Unger et al. as an anticipatory reference for claims 66, 67, 87, 88, 90-94, 135, and 137-139. The Examiner contends that Unger does not teach tenascin (claims 133, 134, 140, 141) or a CMC of about 200 micromolar (claim 89).

The Deficiency of Unger et al.

Applicant's previously submitted arguments are incorporated herein by reference in their entireties. Briefly, as discussed above, Applicants dispute that the disclosures of Unger et al. provide a *prima facie* case of anticipation of claim 66, much less the claims dependent to claim 66, for several reasons. First, Unger et al. do not disclose a specific embodiment that satisfies all of the claim limitations. Second, Unger et al. does not disclose the necessary "pattern of preferences" for a *prima facie* case of anticipation, and instead, the Examiner chooses several elements from the vast disclosure of Unger et al to establish anticipation to the exclusion of considering whether one of ordinary skill in the art would envisage the instant claimed invention in complete and exact terms upon reading Unger et al. Third, Examiner's assumption regarding Unger et al's inherent teaching of a lithium precipitate shell is shown above to be substantially flawed, which Applicant submits specifically renders improper Examiner's *prima facie* anticipation rejection of claims 66 in combination with 138, and of claims 139-141. Fourth, Examiner has not addressed Applicant's argument, grounded by MPEP and case law, that Unger et al's particle size range is not taught with sufficient specificity to anticipate the instant claims.

It is respectfully submitted that the Examiner's has impermissibly used several elements from disparate sections of Unger et al to support this rejection, without any supporting rationale for the selection made. This basis of rejection is contrary to case law in several respects.

First, the Examiner is obligated to determine "whether the claimed invention 'as a whole' would have been obvious" to a person of ordinary skill at the time the invention was made. (MPEP 2142) A mere compilation of elements is not sufficient to establish obviousness; articulating the rationale why a skilled artisan would combine elements to produce the invention in the manner claimed is also relevant.

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known. *(In re KSR v. Teleflex*, 550 U.S. ___, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007))

The KSR decision goes on to describe a basis for determining if there was an apparent reason to combine the known elements in the order of an applicant's claims:

> A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions. Following these principles may be difficult if the claimed subject matter involves more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit. *(In re KSR v. Teleflex, page 4)*

The teaching or suggestion to make the claimed combination must be found outside of the applicant's disclosure. *In re Dembiczak,* 175 F.3d944, 50 USPQ2d 1614 (Fed Cir. 1999). Applicant submits the only basis upon which one skilled in the art could construct an invention of claims 66 and 138 upon reading of Unger et al, would be with the critical knowledge of the Applicant's disclosed invention. Examiner has failed to sufficiently

explain, with a preponderance of evidence and in a manner grounded by case law, why one of ordinary skill in the art would make the designated selections from the vast disclosure of Unger et al, in an attempt to form a composition comprising the elements and order of the instant claims.

Second, Applicant respectfully submits Examiner has also failed to objectively determine whether the skilled artisan's expectation of success is great enough to render a resulting invention obvious. Case law has established that

> an invention would not be invalid for obviousness if the inventor would have been motivated 'to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result**,** where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.' Likewise, an invention would not be deemed obvious if all that was suggested 'was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.' *In re PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 1364 (Fed Cir. 2007), quoting *In re O'Farrell,* see also *In re Medichem, S.A. v. Rolabo, S.L.,* 437 F.3d 1157, 1166-67 (Fed.Cir.2006).

Applicant submits the claimed invention would not have been obvious, nor would it have been assigned a probability of success that would have rendered it obvious, at the time it was made. The state of the art at the time the claimed invention was made viewed endocytosis as an attractive mechanism for targeted drug delivery into the cell. However, with respect to gene delivery for example, while this "seemingly simple concept has been pursued for more than a decade…in practice, this idea has been more difficult to implement effectively than perhaps had been originally anticipated….Effective gene delivery by [the] receptor mediated mechanism requires specific vector binding, internalization, subcellular trafficking, endosomal escape, and unpackaging of the foreign DNA for desired gene expression. While this process offers a noninvasive mechanism to obtain selective intracellular localization of vectors, it may lead to destruction of delivered genes through intracellular pathways"[3], with lysosomal degradation being particularly problematic. With regards to caveolae, "there is to date little quantitative evidence showing caveolae to fulfill

[3] C.M. Varga, et al. "Receptor Mediated Targeting of Gene Delivery Vectors: Insights from Molecular Mechanisms for Improved Vehicle Design", *Biotechnology and Bioengineering*: 70(6) 593-605 (2000).

a role in mediating the uptake of DNA based therapeutics."[4] In view of the above, Applicant submits the cumulative benefits of the present invention, including for example lysosomal avoidance, cargo protection, uniform gene expression, and cell specific delivery, would not have been viewed by one of ordinary skill in the art as having a reasonable chance for being achieved at the time the present invention was made.

In light of the above discussion, the Examiner has not established with a preponderance of evidence that Unger (with Kondo and Schneider) directs one of ordinary skill in the art to the claimed invention, nor has the Examiner established that the skilled artisan's expectation of success would have been great enough to render the claimed invention obvious at the time it was made. Thus, Unger et al does not provide a supportable reference for a *prima facie* rejection of the claimed invention on the grounds of obviousness. This rejection under 35 U.S.C. § 103(a) should be withdrawn and such action is respectfully requested.

Kondo et al and Schneider et al Do Not Provide What Unger et al Lacks

Turning to the 35 U.S.C. § 103(a) rejections of claims 133, 134, 140, 141 or 89, it is submitted that the Unger et al. reference is lacking, and that the references Kondo et al. and Schneider et al. do not remedy the deficiencies of Unger et al.

With respect to the Examiner's assertion on page 19, that "Applicant's argument that modifying the [Unger et al.] particles according to the teachings of Schneider et al. would make them undesirable for their intended purpose is again an argument that is unsupported by any evidence. Unger et al. et al. clearly teaches particle coated with precipitated proteins . . . that are suitable for their method." Applicant traverses this rejection.

The Examiner is respectfully urged to reconsider the arguments provided herein above and the Table on pp. 18-19. Clearly, much evidence has been provided by the Applicant supporting that the intended purpose of the Unger et al. particles is ultrasound applications or therapeutic applications in conjunction with ultrasound. Kindly note that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts

[4]M. Gumbleton, et al. "Caveolae: An Alternative Membrane Transport Compartment", *Pharmaceutical Research:* 17(9) 1035-1048).

necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art". *In re Hedges,* 783 F.2d 1038, 54 USLW 2455, 228 USPQ 685 (Fed. Circ. 1986), citing *In re Wesslau,* 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965).

Legally, it is also established that an invention is not obvious if the inventor would have been motivated 'to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result**,** where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.' Likewise, an invention would not be deemed obvious if all that was suggested 'was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.' *In re PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 1364 (Fed Cir. 2007), quoting *In re O'Farrell,* see also *In re Medichem, S.A. v. Rolabo, S.L.,* 437 F.3d 1157, 1166-67 (Fed.Cir.2006). It is submitted that in the instant case, all that has been provided by the combination of the references is simply an innumerable number of choices, as to which of the possible choices are likely to be successful, in that in particular, Unger et al. teaches that sizes of 200 nm and above are preferred.

It is submitted that the Examiner has failed to sufficiently explain, with a preponderance of evidence and in a manner grounded by case law, why one of ordinary skill in the art would make the designated selections from the vast disclosure of Unger et al, in an attempt to form a composition comprising an ultrasmall particle comprising elements of the instant claims, particularly with respect to claims 133, 134, 140, 141 or claim 89.

It is also pointed out that the Examiner has failed to articulate why the skilled artisan's expectation of success would have been great enough to render the claimed invention, as a whole, obvious at the time it was made. The ultrasmall particles for therapeutic agent delivery as taught by Applicant provide the simultaneous benefits of lysosomal avoidance, cargo protection, uniform gene expression, and cell specific delivery, in which would not have been predictable at the time the present invention was made. The state of the art at the time the claimed invention was made viewed endocytosis as an attractive mechanism for targeted drug delivery into a cell. However, with respect to gene delivery for example, while this "seemingly simple concept has been pursued for more than

a decade…in practice, this idea has been more difficult to implement effectively than perhaps had been originally anticipated….Effective gene delivery by [the] receptor mediated mechanism requires specific vector binding, internalization, subcellular trafficking, endosomal escape, and unpackaging of the foreign DNA for desired gene expression. While this process offers a noninvasive mechanism to obtain selective intracellular localization of vectors, it may lead to destruction of delivered genes through intracellular pathways"[5], with lysosomal degradation being particularly problematic. With regards to caveolae, "there is to date little quantitative evidence showing caveolae to fulfill a role in mediating the uptake of DNA based therapeutics."[6] Accordingly, since these benefits were not predictable at the time the invention was made, these benefits were unappreciated by the Unger et al, Schneider, and Kondo references and thus there is no teaching, suggestion or prediction that such particles would be successful, particularly with respect to claims 133, 134, 140, 141 or claim 89.

Reconsideration is respectfully requested.

Kondo et al, Medina, Quay, or Duquemin et al Do Not Provide What Unger et al Lacks

Claims 66, 67, 87, 88, 90-94, and 135-139 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Unger et al taken with Kondo et al., in view of each Medina (U.S. Patent No. 5,650,543, of record), Quay (U.S. Patent No. 5,707,606, of record) and Duquemin et al (J Pharm Pharmacol, 1985, 37: 698-702, Abstract). See Office Action at page 20.

Applicant's previously submitted arguments from previous Office Action responses are incorporated herein by reference in their entireties, and Applicant's arguments with respect to Unger et al. in the rejection over Unger et al. taken with Kondo et al., in view of Schneider et at ÷ Briefly, as discussed above, Applicants dispute that the disclosures of Unger et al. provide a *prima facie* case of anticipation, for the reason that not only does Unger et al. not disclose a specific embodiment that satisfies all of the claim limitations, Unger et al. does not disclosed the required "the pattern of preferences" for a *prima facie* case of anticipation. Applicant also submits Examiner's argument of Unger et al teaching a

[5] C.M. Varga, et al. "Receptor Mediated Targeting of Gene Delivery Vectors: Insights from Molecular Mechanisms for Improved Vehicle Design", *Biotechnology and Bioengineering*: 70(6) 593-605 (2000).
[6] M. Gumbleton, et al. "Caveolae: An Alternative Membrane Transport Compartment", *Pharmaceutical Research:* 17(9) 1035-1048).

lithium precipitate is significantly flawed from a basic science perspective, and that Examiner has not addressed Applicant's argument that Unger et al particle size range is not taught with sufficient specificity to anticipate the instant claims. Applicant respectfully submits Examiner's choosing of several elements from the vast disclosure of Unger et al is not sufficient to establish anticipation to the exclusion of considering whether one of ordinary skill in the art would envisage the instant claimed invention in complete and exact terms upon reading Unger et al.

In particular, the Examiner states that deficiencies of Unger et al., with respect to claim 136, are made up by Medina and Quay in view of Duquemin.

Applicant incorporates by reference the arguments provided previously.

The Examiner is respectfully urged to reconsider the arguments provided herein above and the Table on pp. 18-19. Clearly, much evidence has been provided by the Applicant supporting that the intended purpose of the Unger et al. particles is ultrasound applications or therapeutic applications in conjunction with ultrasound. Applicant's ultrasmall particles, as discussed in Applicant's September 26, 2007 Response, will not work in ultrasound applications or in conjunction with ultrasound applications. Kindly note that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art". *In re Hedges,* 783 F.2d 1038, 54 USLW 2455, 228 USPQ 685 (Fed. Circ. 1986), citing *In re Wesslau,* 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965).

Legally, it is also established that an invention is not obvious if the inventor would have been motivated 'to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result**,** where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.' Likewise, an invention would not be deemed obvious if all that was suggested 'was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.' *In re PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 1364 (Fed Cir. 2007), quoting *In re*

O'Farrell, see also *In re Medichem, S.A. v. Rolabo, S.L.,* 437 F.3d 1157, 1166-67 (Fed.Cir.2006). It is submitted that in the instant case, all that has been provided by the combination of the references is simply an innumerable number of choices, and that the art actually gives misdirection (in terms of the instant invention) as to which of the possible choices are likely to be successful, in that in particular, Unger et al. teaches that sizes of 200 nm and above are preferred.

It is submitted that the Examiner has failed to sufficiently explain, with a preponderance of evidence and in a manner grounded by case law, why one of ordinary skill in the art would make the designated selections from the vast disclosure of Unger et al, in an attempt to form a composition comprising an ultrasmall particle comprising elements of the instant claims, and combine with Medina and Quay in view of Duquemin particularly with respect to claim 136.

It is also pointed out that the ultrasmall particles for therapeutic agent delivery as taught by Applicant provide the unexpected benefits of lysosomal avoidance, cargo protection, uniform gene expression, and cell specific delivery, in contrast to the teachings of the art at the time the present invention was made. The state of the art at the time the claimed invention was made viewed endocytosis as an attractive mechanism for targeted drug delivery into a cell. However, with respect to gene delivery for example, while this "seemingly simple concept has been pursued for more than a decade…in practice, this idea has been more difficult to implement effectively than perhaps had been originally anticipated….Effective gene delivery by [the] receptor mediated mechanism requires specific vector binding, internalization, subcellular trafficking, endosomal escape, and unpackaging of the foreign DNA for desired gene expression. While this process offers a noninvasive mechanism to obtain selective intracellular localization of vectors, it may lead to destruction of delivered genes through intracellular pathways" [7], with lysosomal degradation being particularly problematic. With regards to caveolae, "there is to date little quantitative evidence showing caveolae to fulfill a role in mediating the uptake of DNA based therapeutics." [8] Accordingly, since these benefits were unknown at the time

[7] C.M. Varga, et al. "Receptor Mediated Targeting of Gene Delivery Vectors: Insights from Molecular Mechanisms for Improved Vehicle Design", *Biotechnology and Bioengineering*: 70(6) 593-605 (2000).
[8]M. Gumbleton, et al. "Caveolae: An Alternative Membrane Transport Compartment", *Pharmaceutical Research:* 17(9) 1035-1048).

the invention was made, these benefits were unappreciated by the Unger et al, Medina and Quay in view of Duquemin references and thus there would be no teaching, suggestion or prediction that such particles would be successful, particularly with respect to claim 136.

Reconsideration is respectfully requested.

For the reasons set forth above, Applicant respectfully submits the claims as filed are allowable over the art of record and reconsideration and issuance of a notice of allowance are respectfully requested. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for a three-month extension of time pursuant to 37 C.F.R. § 1.136(a) and an authorization to charge all fees therefor to deposit account No. 19-5117. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

Date: June 11, 2008

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